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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/487,023 | 01/19/2000 | Parkash S. Gill | 21327-701 CIP | 2622 |

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| EXAMINER | |
|---|---|
| MCGARRY, SEAN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/487,023 | GILL ET AL. | |
| | Examiner | Art Unit | |
| | Sean R. McGarry | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,9-12,16,20,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9, 9-12, 16, 20, 24, and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 9-12, 16, 20, 24, and 25 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-7, 9, and 10 of U.S. Patent No. 6, 291,667 in view of Uchida et al [US 6,150,092].

The claimed invention is drawn to antisense oligonucleotides, SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28, and 29, which have phosphorothioate modifications. The antisense oligonucleotides all target within a region corresponding to nucleotides 259-293 of VEGF.

The oligonucleotide of 6,291,667 targets a region corresponding to nucleotides 261-293 of VEGF.

The antisense oligonucleotides of the instant application render the antisense oligonucleotide of the patent obvious since these oligonucleotides represent a class of

oligonucleotides targeting a small region of VEGF where the antisense oligonucleotide of the patent is targeted within that same region. The antisense oligonucleotides of the instant application all overlap SEQ ID NO: 2 of the patent.

Furthermore, Uchida et al have taught methods of inhibiting VEGF with antisense oligonucleotides. The antisense oligonucleotides claimed by Uchida et al are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. This region is 42 nucleotides long and is taught to be a preferred region on VEGF to target. All of the specifically recited antisense oligonucleotides of instant claims 2, 10, 12,16, and 24, and SEQ ID NO: 2 of the patent, for example, are all targeted to SEQ ID NO: 7 as taught by Uchida et al. The region taught by Uchida et al., is relatively small at 42 nucleotides in length. All of the recited antisense oligonucleotides of instant claims 2, 10, 12, 16 and 24, and SEQ ID NO: 2 of the patent overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example). Uchida et al have taught that the region defined by SEQ ID NO:7, to which all of the claimed oligonucleotides are targeted, is a desirable region to target and is even referred to as a "core region" for targeting VEGF with antisense. Uchida et al further disclose pharmaceutical preparations for treatment of disease throughout their specification and claims. At columns 4 and 8-9 of Uchida et al, for example, pharmaceutical compositions, including various liposomal compositions, and methods of treatment with VEGF antisense oligonucleotides with phosphorothioate linkages are disclosed.

The antisense oligonucleotides of the instant application are therefore obvious variants of the antisense oligonucleotide, SEQ ID NO: 2, claimed in 6,291,667.

Applicant's arguments filed 4/18/06 have been fully considered but they are not persuasive. Applicant's arguments do not specifically address this ground of rejection and the rejection is maintained for the same reasons of record.

Claims 2, 9-12, 16, 20, 24, and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al [6,150,092] and Robinson et al [5,814,620; 5,710,136; and, 5,801,156].

The claimed invention is antisense oligonucleotides and compositions comprising antisense oligonucleotides for the inhibition of VEGF where the antisense oligonucleotides are selected from SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28, and 29.

Uchida et al have taught methods of inhibiting VEGF with antisense oligonucleotides. The antisense oligonucleotides claimed by Uchida et al are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. This region is 42 nucleotides long and is taught to be a preferred region on VEGF to target. All of the specifically recited antisense oligonucleotides of instant claims 2, 10, 12,16, and 24, for example, are all targeted to SEQ ID NO: 7 as taught by Uchida et al. The region taught

by Uchida et al., is relatively small at 42 nucleotides in length. All of the recited antisense oligonucleotides of instant claims 2, 10, 12, 16 and 24 overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example). See diagram attached to the Official Action mailed 8/5/05 which shows the context of the prior art teachings of antisense to VEGF and the antisense oligonucleotides of the instant invention. Uchida et al have taught that the region defined by SEQ ID NO:7, to which all of the claimed oligonucleotides are targeted, is a desirable region to target and is even referred to as a "core region" for targeting VEGF with antisense. Uchida et al further disclose pharmaceutical preparations for treatment of disease throughout their specification and claims. At columns 4 and 8-9 of Uchida et al, for example, pharmaceutical compositions, including various liposomal compositions, and methods of treatment with VEGF antisense oligonucleotides with phosphorothioate linkages are disclosed.

Robinson et al, in all of the three cited references, has demonstrated that antisense oligonucleotides targeted to VEGF have been known for use in various methods of treatment prior to applicant's invention. It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier, including liposomes (see 5,814,620, columns 9 and 11, for example) and phosphorothioate modifications (see columns 3, 7, 8, 12 and claims 3 and 4, of 5,814,620, for example).

Applicants claim limitations of a particular $IC_{50}$ is not seen as providing a difference between the prior art antisense and that instantly claimed since no particular conditions for the cell cultures in the determination of such a value are required by the claims. This allows one in the art to set the conditions such that a particular IC50 value may be observed.

One in the art would clearly have had motivation to make the instantly claimed antisense molecules since it is absolutely clear that the region targeted has been clearly shown by the prior art to be a desired target for antisense inhibition of VEGF. One in the art would clearly look to the SEQ ID NO: 7 region in the making of antisense targeted to VEGF and the optimization of antisense to VEGF, for example. The specific antisense claimed are not only targeted to the specifically taught target sequence but many overlap, embrace or are embraced by the specific VEGF antisense taught by Uchida et. One in the art would clearly look to these specific regions to make antisense oligonucleotides to inhibit VEGF since the specific region has clearly been shown to be an effective target region and antisense to this target have been clearly taught in the art to be effective antisense oligonucleotides. One in the art would clearly look to the region taught by Uchida to be a "core region" for antisense targeted to VEGF to optimize antisense targeted to VEGF, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 21-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al., Robinson et al [US 5,814,620], Barleon et al [Blood Vol. 87, No. 8:3336-3343, 4/15/96] and Chan et al [The American journal of Surgical Pathology Vol. 22(7):816-826, 1998].

Uchida et al is relied upon as above and further for the following: It has been taught at column 1, for example, that ". . .inhibition of the vascular endothelial growth factor leads to inhibition of growth of solid tumor cells, and this should be applicable in the development of anticancer agents. [I]n fact there is a report on a method to use an anti-VEGF antibody"

Robinson et al has demonstrated that antisense oligonucleotides targeted to VEGF have been known for use in various methods of treatment prior to applicants invention and that it was known to use liposome formulations for pharmaceutical preparations of antisense oligonucleotides (see column 9, for example). It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier. It is further taught that such compositions can include other factors and/or agents which enhance inhibition of VEGF expression or which will reduce neovascularation (see columns 8 and 9, for example). It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier. It is further taught that such compositions can include other factors and/or agents which enhance inhibition

of VEGF expression or which will reduce neovascularation (see columns 8 and 9, for example).

Barleon et al taught inhibition of VEGF via specific antiserum and the role of flt-1 with VEGF biopathway.

Chan et al have taught the Association of VEGF and its receptors and their roles in various diseases.

Applicants claim limitations of a particular $IC_{50}$ is not seen as providing a difference between the prior art antisense and that instantly claimed since no particular conditions for the cell cultures in the determination of such a value are required by the claims. This allows one in the art to set the conditions such that a particular IC50 value may be observed.

It would have been obvious to use antibodies in conjunction with antisense targeted to VEGF since the prior art has taught antisense to inhibit VEGF, antibodies to inhibit VEGF and since the art has taught that VEGF receptors are associated with the same disease sates as VEGF. The art has taught that one in the art can combine other VEGF inhibitors in combination with VEGF antisense. Since the art has shown inhibition of VEGF by antisense and via antibodies one in the art would have a reasonable expectation of the successful use of a combination of such a combination and further to simply combine different antisense targeted to the same target, for example. Furthermore it is prima facie obvious to combine two composition each of which has been taught in the art to be useful for the same purpose (see MPEP2144.06, for example).

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

The examiners response to Applicant's arguments filed 8/4/05 are repeated below.

The Declarations of Parkash Gill and Ruiwen Zhang, filed 8/04/05, have been considered but the weight of the evidence provided in those declarations is of insufficient weight to overcome the rejections of record. The declarations provide the same content and will be treated in one discussion. The declarations are opinion declarations that assert that, in the opinion of the Declarants, one in the art would not be motivated to use phosphorothioate modifications based on the disclosure of Uchida et al. Both assert that they have read the previous official action and have reviewed the Uchida et al Patent. It is asserted that phosphorothioate-modified antisense are designed for use in *in vivo* or cell-based applications and assert that one would only be motivated to make such if one intended to use the antisense in cells or in vivo. It is asserted that the cell-free assays of Uchida et al show many instances of inhibition of over 90%. It is then asserted that the cell based assays of Uchida et al showed less inhibition of VEGF and also assert that the concentration used in the assays could provide non-specific antisense effects, although no evidence of such is provided. It is then asserted that in their comparison of the cell-free to cell based assays there is a poor correlation and conclude that there is no reason to expect that any of the antisense

that Uchida et al identified in their cell free assay would be likely to be effective as PS-modified antisense.

In response it is noted that neither declaration provides any data to dispute the teachings of Uchida et al. It is agreed that PS-modified oligonucleotides are used for cell based and *in vivo* applications to protect from nuclease degradation. One in the art would not expect a modified oligonucleotide to function the same as an unmodified oligonucleotide since the modifications are made to function in a different environment ie a cellular environment. The Declarants appear to assert that the PS-modified antisense of Tables 8 and 9 of Uchida et al are not effective. Applicant is directed to column 25 and 26 of Uchida et al. Uchida et al disclose that the oligonucleotide shown in Table 9 are in fact considered effective and further assert that the phosphorothioate-type oligodeoxyribonucleotides having the nucleotide sequences selected in the screening in the cell free system can be used to inhibit the expression of VEGF in cultured cells as well (column 25, lines50-column 26, lines 3, for example). Uchida et al then further demonstrate the use of PS-modified antisense in an *in vivo* experiment where phosphorothioate antisense treated tumors were smaller than tumors not treated. Uchida disclose that phosphorothioate-type oligodeoxyribonucleotides selected by screening in the cell-free and cultured-cell systems can be used to inhibit tumor growth in experimental animals. Uchida further disclose ". . . the antisense nucleic acid having a nucleotide sequence complementary to at least 8 or more nucleotides in the core region is useful as a therapeutic agent. . ." (see column 26, for example).

Applicant argues in their response filed 8/04/05 that there is no suggestion to modify the sequences of any of the sequences of Uchida to arrive at any of the specific sequences now claimed. It has been repeatedly asserted by the examiner that the fact that Uchida et al have taught the "core" region of SEQ ID NO:7, and further claims antisense targeted to the region of SEQ ID NO: 7, is in itself motivation to make them. The small region [SEQ ID NO:7] has been taught to be a core region to target where one in the art has been specifically directed to make antisense to this region, which is the same region that the instantly claimed oligonucleotides are targeted. Applicant asserts that there is no motivation to modify the instant antisense to include phosphorothioate modifications. Uchida et al teach using phosphorothioate modifications for *in vivo* and cellular use, as do all three of the Robinson references. Applicant also asserts that one would have no reasonable expectation that phosphorothioate antisense molecules would function in cells. It is clear from the discussion in the above paragraph that clearly there is at least a reasonable expectation of success.

Even though the specific sequences claimed have not been specifically disclosed they are indeed variations on what has been taught in the art. Again it is noted that applicant has not provided any evidence that the specific antisense claimed have any activity that would be unexpected over what has been taught in the prior art. A review of the Attachment, provided in the Official Action mailed 8/05/04, shows a clear picture of how small the target region is and how applicants' specific sequences are all meshed within the specific target region taught by Uchida and the specific antisense

oligonucleotides of Uchida. It is noted that the diagram in the Attachment is not an exhaustive comparison, but still provides a clear picture of the instantly claimed oligonucleotides in comparison to that taught in the art. Uchida et al and Robinson have both taught phosphorothioate modifications and have taught how they are beneficial for use in therapeutic applications. The art has clearly shown a motivation to modify antisense oligonucleotides for use in therapies, for example. It is clear that Uchida et al intended for their antisense oligonucleotides to be used in vivo. Applicant argues that the antisense modified by Uchida et al do not work well in cells. This is merely an opinion with no data (i.e. comparative: this point of comparative analysis between the prior art and the instant compounds has been made by the examiner in all answers to applicant arguments) that would show that this would be fact. Applicant's argument as to the "poor effectiveness" of the antisense of Uchida as compared to the antisense instantly claimed antisense has not been demonstrated. Applicant does not compare that which can be properly compared. A side-by-side analysis of those antisense in the art and those specifically claimed would provide a better position for the determination of any unexpected results. As the record stands there are not unexpected properties shown for the instantly claimed oligonucleotides compared to those taught in the prior art. Applicant repeatedly asserts that the antisense of Uchida et al do not work but have provided nothing more than opinion. Applicant for example points to Table 9, SEQ ID NO:51 of Uchida et al and asserts that the cell free assay using a non-phosphorothioate inhibited more than the phosphorothioate SEQ ID NO: 51 in a cell based assay, however Uchida et al assert that this specific antisense SEQ ID NO: 51 is effective as a

PS-modified oligo (see column 25, lines 50-65, for example. Applicant asserts that Robinson fails to fill the gap between the teachings of Uchida et al and the instant invention. It is noted that Uchida et al have taught phosphorothioates and the Robinson references demonstrate that VEGF antisense and especially PS-modified antisense to VEGF have been clearly shown to work in various *in vivo* methods and provides a clear picture that one would expect PS-modified oligonucleotides to function *in vivo*. Applicants invention appears to be an optimization of that taught in Uchida et al.

Applicant argues against the Robinson and Barleon references of the second 103 rejection of record by asserting that neither of them teaches a combination of antibody and antisense. It is noted that that is why the remainder of the references are present in the rejection. The remainder of the arguments are based on the same reasons argued above.

Applicant's arguments filed 4/18/06 have been fully considered but they are not persuasive.

Applicant argues essentially that the examiner should reconsider the credibility of the Uchida patent disclosure. Again, applicant offers nothing in the way of evidence to show that any assertion of Uchida is not accurate. Applicant asserts that the examiner should give more weight to the opinion of Dr Zhang. It is noted that the declaration of Dr. Zhang provides only opinion and does not provide any evidence in the way of data or in the way of argument that might show by correlation that the conclusions of Uchida are not accurate. The examiner has not dismissed the declarations of Dr, Gill and Dr.

Zhang, but has determined that the weight of evidence provided in them is insufficient to show the instant invention is not obvious over the prior art. The examiner has not requested or required comparative data but has pointed out that such evidence would be considered in the determination of obviousness.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
Primary Examiner
Art Unit 1635